Amendments to the Specification:

Please replace paragraph **[0014]** with the following paragraph:

-- **[0014]** In a preferred embodiment, the promoter is an RNA polymerase II promoter. For example, particularly preferred promoters for use in the invention include collagen 1A1 promoters, collagen 1A2 promoters, collagen 3A1 promoters, cone transducin alpha subunit GNAT-2 promoters, peripherin-retinal degeneration slow (rds) promoters, rhodopsin promoters, cone arrestin promoters, RPE65 promoters, Thyrotropin releasing hormone (TRH) promoters, THR-degrading ecotoenzymes promoters, TRH receptor promoters, albumin promoters, insulin promoters, Huntington's promoters, presenillin 1 and 2 promoters, superoxide dismutase (SOD) promoters, and enolase promoters (Table ~~2~~1). --

Please replace paragraph **[0031]** with the following paragraph:

-- **[0031]** According to a third aspect of the present invention, there is provided [[a]] host cells comprising the polynucleotide of the first aspect of the invention or the vector according to the second aspect of the invention. The polynucleotide is preferably integrated into the host cell genome. --

Please replace paragraph **[0042]** with the following paragraph:

-- **[0042]** Figure 2 shows exemplary RNAi constructs carrying an RNAi sequence ~~to be expressed adjacent~~and one or more TSSs of a tissue specific and/or cell specific and/or general and/or inducible promoter and/or control sequence. The contructs may also optionally include additional cleaving element(s). ~~Also shown is a construct carrying a promoter fused to a RNAi sequence close or at one or more TSSs of the promoter together with a cis-acting ribozyme 3' of the RNAi sequence to be expressed.~~ --

Please replace paragraph **[0044]** with the following paragraph:

-- **[0044]** Figure 4A shows the design of an RNAi targeting enhanced green fluorescent protein (EGFP) in linear and hairpin forms ~~and a non-targeting RNAi control~~ (residues 71 to 125 of SEQ ID NO: 1). Figure 4B shows the design of an RNAi targeting EGFP ~~and a non-targeting RNAi control~~ with cis-acting hammerhead ribozymes 5' (residues 29 to 72 of SEQ ID NO: 1) and 3' (residues 121 to 168 of SEQ ID NO: 1) of the RNAi sequence. ~~Arrows highlight ribozyme cleavage sites.~~ Figure 4C shows the design of the 5'/3' ribozyme-EGFP RNAi cassette when driven by a cytomegalovirus (CMV) ~~CMV~~ promoter and cloned into pcDNA3.1 (Invitrogen- Cat.# V79520). Figure 4D shows sequence from the pCDNA3.1 vector containing 5' and 3' cis-acting ribozymes with RNAi targeting EGFP (SEQ ID NO: 12). Figure 4E shows sequence from the pcDNA3.1 vector carrying 5' and 3' cis-acting ribozymes and the non-targeting RNAi control sequence (SEQ ID NO: 13). Table ~~1~~ 2 provides sequences for oligonucleotides that were utilized to generate ribozyme-RNAi constructs. Figure 4F shows sequence from pcDNA3.1 with the H1 promoter driving expression of RNAi targeting EGFP (SEQ ID NO: 14). Figure 4G shows sequence from the pcDNA3.1 vector carrying sequence for the rat albumin promoter (SEQ ID NO: 15). --

Please replace paragraph **[0054]** with the following paragraph:

-- **[0054]** Promoters that may be used in the present invention include, but are not limited to collagen 1A1, collagen 1A2, GNAT-2, peripherin-rds, rhodopsin, retinal pigment epithelium 65 (REP65) promoters, cone arrestin promoters, albumin, insulin, huntington, collagen3A1, super oxide dismutase promoters, presenillin1 and 2 promoters, enolase promoters. (See Tables ~~2~~1A, 1B, and 1C) --

Please replace Table 2A and its heading with the following table and heading:

-- Table ~~2~~1A. List of Genes (abbreviations and in full) with promoters that may be used in the invention to drive tissue specific expression of RNAi.

Gene	Gene name in full
ABCA4	ATP-binding cassette transporter
ABO	Blood group antigen
ADA	Adenosine deaminase deficiency
ADRB3	Beta-3 adrenergic receptor
AIPL1	Aryl hydrocarbon receptor-interacting protein-like 1
ALB	Albumin
ALDH (1B1, 2, 4, 9, 3A1, 3A2)	Aldehyde dehydrogenase (1B1, 2, 4, 9, 3A1, 3A2)
APC	Adenomatous polyposis coli
AR	Androgen receptor
AT3	Antithrombin
ATM	Ataxia-telangiectasia
BCP	Blue cone pigment
BLM	Bloom syndrome
BRCA1	Breast cancer 1
BRCA2	Breast cancer 2
CDKN2A	Cyclin-dependent kinase inhibitor
CFTR	Cystic fibrosis
CHS1	Chediak-Higashi syndrome
CLN (1, 2, 3, 5, 8)	Ceroid lipofuscinosis
CNGA1	Cyclic nucleotide-gated cation channel 1
CNGA3	Cyclic nucleotide-gated cation channel 3
COL1A1, COL1A2, COL3A1	Collagen (types I and III)
CRB1	Crumbs homologue 1
CRX	Cone rod homeobox
CYBA	Chronic granulomatous disease

CYBB	X-linked chronic granulomatous disease
DMD	Duchenne muscular dystrophy
EMD	Emery-Dreifuss muscular dystrophy
FANCA, FANCC	Fanconi anaemia
FBN1	Fibrillin 1
FBN1	Fibrillin 2
F7	Factor VII
F8	Factor 8
F9	Factor 9
GAA	Acid alpha-glucosidase
GCH1	GTP cyclohydrolase I deficiency
GCP	Green cone pigment
GNAT1	Transducin, alpha rod subunit
HEXA	Hexosaminidase A
HEXB	Hexosaminidase B
HPS	Hermansky-Pudlak
L1CAM	L1 cell adhesion molecule
MEFV	Mediterranean fever
MEN1	Multiple endocrine neoplasia 1
MYO7A	Myosin VIIa
NAT1, NAT2	Arylamine N-acetyltransferases
NBS1	Nijmegen breakage syndrome 1
NCF1	Chronic granulomatous disease 1
NCF2	Chronic granulomatous disease 2
NF1	Neurofibromatosis type 1
NF2	Neurofibromatosis type 2

NR2E3	Photoreceptor cell-specific nuclear receptor
NRL	Neuroretina-linked leucine zipper
NYX	Nyctalopin
OA1	Ocular albinism 1
OCA2	Ocular albinism 2
OTC	Ornithine transcarbamylase deficiency
PAH	Phenylketonuria
PCBD	Pterin-4a-carbinolamine dehydratase deficiency
PDC	Phosducin
PDE6A, PDE6B	Phosphodiesterase type 6
PLP	Proteolipid protein
PPT1	Palmitoyl-protein thioesterase
PRKCG	Protein kinase C gamma
PRNP	Prion Protein
PROC	Protein C
PROS	Protein S
PROML1	Prominin (mouse)-like 1
PSEN1, PSEN2	Presenilin 1 and Presenilin 2
PTS	6-Pyruvoyl-tetrahydropterin synthase deficiency
QDPR	Dihydropteridine reductase deficiency
RB1	Retinoblastoma
RBP4	Retinol-binding protein 4
RCP	Red cone pigment
RDH5	11-cis retinol dehydrogenase
RDS	Retinal degeneration, slow
RGR	RPE-retinal G-protein-coupled receptor

RHO	Rhodopsin
RHOK	Rhodopsin kinase
RLBP1	Cellular retinaldehyde-binding protein
ROM1	Rod outer membrane protein 1
RP1	Retinitis pigmentosa 1
RP2	Retinitis pigmentosa 2
RPE65	Retinal pigment epithelium specific protein
RPGR	Retinitis pigmentosa GTPase regulator
RS1	Retinoschisis 1
SGCA	Sarcoglycan-alpha
SGCB	Sarcoglycan-beta
SGCG	Sarcoglycan-gamma
SGCD	Sarcoglycan-delta
TIMP3	Tissue inhibitor of metalloproteinase 3
TSC1	Tuberous sclerosis 1
TSC2	Tuberous sclerosis 2
TTR	Transthyretin
TULP1	Tubby-like protein 1
TYR	Tyrosinase
TYRP1	Tyrosinase-related protein 1
USH2A	Usher syndrome 2A
VHL	Von Hippel-Lindau
VMD2	Vitelliform macular dystropy
VWF	Von Willebrand disease
WRN	Werner syndrome
WT1	Wilm's tumour

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Please replace the Table 2B heading with the following table heading:

-- Table ~~2~~1B. List of Inducible Promoters that may be used to drive inducible expression of RNAi. --

Please replace the Table 2C heading with the following table heading:

-- Table ~~2~~1C: List of genes with promoters that can be utilized to drive tissue and/or cell specific expression of RNAi --

Please replace paragraph **[0059]** with the following paragraph:

-- **[0059]** Promoters for use in the practice of the invention may be inducible promoters. Such promoters are well known in the art and include for example, tetracycline inducible promoters, hyperthermia-inducible human heat shock protein-70 (hsp70) promoter, glial fibrillary acidic protein (GFAP) promoter and human interferon (IFN)-inducible MxAX (Table ~~2~~1) (Sakai, 2002; Utomo, 1999). Such promoters enable inducible expression of RNAi constructs with one or more cis-acting cleaving elements that cleave 5' and/or 3' of the RNAi. --

Please replace paragraph **[0095]** with the following paragraph:

-- **[0095]** The invention further provides methods and assays which may be used to identify candidate modulators of gene expression. In a preferred embodiment, the invention provides a method of identifying a modulator of a target gene, the method comprising the steps: (i) providing a host cell of the invention or a transgenic organism of the invention, (ii) administering a candidate modulator to the host cell or said transgenic organism, and (iii) determining expression of the target gene in the presence of the candidate modulator. --

Please replace paragraph **[0098]** through the heading for paragraph **[0099]** with the following paragraph:

-- **[0098]** Figures ~~1A, 1B~~ 2A, 2B, and 4 provide an overview of the method to generate RNAi expressed from a tissue specific and/or cell specific and/or inducible promoter.

~~Table~~Tables ~~1~~2A and 2B provide[[s]] sequences for RNAi targeting EGFP and a non-targeting RNAi control. The particular RNAi targeting EGFP utilized has previously been shown to be functional in cells and *in vivo* and has been used by Hasuwa et al. (2002) and others for this purpose. Tables ~~1~~2A and ~~1~~2B provide[[s]] sequences for RNAi targeting EGFP flanked by 5' and 3' cis-acting ribozymes and a non-targeting RNAi control flanked by 5' and 3' cis-acting ribozymes. --

Please replace Table 1A and its heading with the following table and heading:

-- Table ~~1~~2A: RNAi sequences

R2D2egfp

GGCTAGCTAGCTCTAGAGGATCCGTGGTTGCTGATGAGTCCGTGAGGA
CGAAACGGTACCCGGTACCGTCCAACCACTACCTGAGCACCCAGTTCA
AGAGACTGGGTGCTCAGGTAGTGGTTGTCGACGGATCATGATCCGTCC
TGATGAGTCCGTGAGGACGAAACAACCACGAATTCAAGCTTGACCTCT
CGAC (SEQ ID NO: 1)

Nucleotides 6-23 are [[a]] restriction enzyme sites; nucleotides 24-30 are an arm of the ribozyme binding to ~~hair pin~~hairpin RNAi; ~~nucleotide~~nucleotides 31-70 are a ribozyme, nucleotides 71-125 are a hairpin RNAi; nucleotides 126-166 ~~is~~are a ribozyme[[)]]; nucleotides 167-173 ~~is~~are the arm of a ribozyme binding to hairpin RNAi; nucleotides 174-185 ~~is~~are [[a]] restriction enzyme ~~digest site~~sites.

R2D2xera

GGCTAGCTAGCTCTAGAGGATCCCTTGCCGCTGATGAGTCCGTGAGGA
CGAAACGGTACCCGGTACCGTCCGGCAAGCTGACCCTGAAGTTCTTCA
AGAGAGAACTTCAGGGTCAGCTTGCCGTAGACGGATCATGATCCGTCC
TGATGAGTCCGTGAGGACGAAACGGCAAGGAATTCAAGCTTGACCTCT

CGAC (SEQ ID NO: 2)

Nucleotides 6-23 are [[a]] restriction enzyme sites; nucleotides 24-30 are an arm of the ribozyme binding to ~~hair pin~~hairpin RNAi; ~~nucleotide~~nucleotides 31-70 are a ribozyme, nucleotides 71-125 are a hairpin RNAi; nucleotides 126-166 ~~is~~are a ribozyme[[)]]; nucleotides 167-173 ~~is~~are the arm of a ribozyme binding to hairpin RNAi; nucleotides 174-185 ~~is~~are [[a]] restriction enzyme ~~digest site~~sites.

R2D2Non

GGCTAGCTAGCTCTAGAGGATCCCGGAGAACTGATGAGTCCGTGAGG

ACGAAACGGTACCCGGTACCGTCTTCTCCGAACGTGTCACGTTTCAAG

AGAACGTGACACGTTCGGAGAATTGACGGATCATGATCCGTCCTGATG

AGTCCGTGAGGACGAAATTCTCCGGAATTCAAGCTTGACCTCTCGAC

(SEQ ID NO: 3)

Nucleotides 6-23 are [[a]] restriction enzyme ~~site~~sites; nucleotides 24-30 are an arm of the ribozyme ~~bending~~binding to hairpin RNAi; nucleotides 31-70 are a ribozyme; nucleotides 71-119 are a hairpin RNAi; nucleotides 126-160 ~~is~~are a ribozyme; nucleotides 161-167 ~~is~~are the arm of a ribozyme ~~bending~~binding to hairpin RNAi; nucleotides 168-179 ~~is~~are [[a]] restriction enzyme ~~digest site~~sites. --

Please replace paragraph **[0099]** with the following paragraph:

-- **[0099]** Three ribozyme-RNAi constructs are designed, PCR amplified and cloned into pCDNA3.1 (-). Two constructs contain RNAi sequences homologous to EGFP RNA, the third construct contains a non-targeting control RNAi sequence (which is not homologous to any known mammalian transcripts). 1. EGFP targeting construct 1 (R2D2xera). 2. EGFP targeting construct 2 (R2D2egfp). 3. Non-targeting construct (R2D2non) (Table ~~1~~2A).
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Please replace paragraph **[0100]** with the following paragraph:

-- **[0100]** Primers for PCR amplification of RNAi sequences contain restriction enzyme sites to enable cloning of resulting DNA fragments into multiple vectors. The forward PCR primer (R2D2For-) contains Nhe1, Xba1 and BamH1 restriction enzyme sites. The reverse PCR primer (R2D2Rev) contains Hind111 and EcoR1 restriction enzyme sites. The same primers were used to PCR amplify each of the three ribozyme-RNAi constructs. Overlapping oligonucleotides were used as PCR templates for the three R2D2 ribozyme-RNAi constructs (Table ~~1~~2B). --

Please replace the heading for Table 1B after paragraph **[0100]** with the following underlined heading:

-- Table ~~1~~2B: Sequence of oligonucleotides for PCR reactions and RNAi constructs are provided: --

Please replace paragraph **[0104]** with the following paragraph:

-- **[0104]** Figure 5A shows the design of a liver specific ribozyme EGFP RNAi construct. The rat albumin promoter drives tissue specific expression in liver cells; (Postic et al. (1999) J Biol Chem 274: 305). The rat albumin promoter is active in mice expressing a promoter-gene construct. Promoters previously shown to elicit tissue specific expression of sequences placed 3' of the promoter sequence are used to generate constructs containing RNAi targeting EGFP and non-targeting RNAi controls. Constructs also include one or more cis-acting ribozymes 5' and/or 3' of the RNAi sequence (see Example 1 for sequences of ribozyme-RNAi cassettes). 2.3kb of the albumin promoter/enhancer sequence (Postic et al. J Biol Chem 274: 305 1999) is cloned into pcDNA3.1- (Invitrogen) using Not1 and BamH1 restriction enzyme sites in the multiple cloning site (MCS) of the vector. Cis-acting ribozyme-RNAi sequences (Tables ~~1~~2A and 2B) are cloned 3' of tissue

specific promoter sequences using BamH1 and Hind111 restriction enzyme sites (Figure 5A). --

Please replace paragraph **[0107]** with the following paragraph:

-- **[0107]** Figure 5C shows the design of a photoreceptor specific ribozyme EGFP RNAi construct. Photoreceptor specific expression of reporter genes can be achieved using promoters defined in cell culture and *in vivo*. For example, the GNAT-2 promoter and IRBP enhancer drives gene expression in cone photoreceptor cells and is expressed in a number of cone-derived cell lines (for example, Y79 cells). 280 bases of the GNAT-2 promoter and 220 bases of the IRBP enhancer (Accession Number: J03912; M22453) are cloned into the MCS of pcDNA3.1- using Xba1 restriction enzyme sites (Figure 5) The IRBP enhancer is cloned into the same construct using BamH1 restriction enzyme sites. 5' and 3' cis-acting ribozyme-EGFP RNAi sequences (Tables ~~1~~2A and 2B) are cloned 3' of tissue specific promoter sequences using Xba1 and EcoR1 restriction enzyme sites. 661W cells and Y79 cells are assayed for GNAT-2 expression using rt-PCR and standard methods. Additionally, cell lines from tissues other than the retina, for example, from hepatocytes, liver-derived cells, are assayed for GNAT-2 expression by rt-PCR. Specific cell types in which the GNAT-2 gene is not expressed are confirmed. The GNAT-2 promoter cis-acting ribozyme EGFP RNAi constructs are transfected into photoreceptor-derived cell lines expressing GNAT-2 (for example, Y79 cells) and into non-photoreceptor-derived cell lines that do not express GNAT-2 (for example, hepatocytes). Cell lines transfected with tissue specific ribozyme RNAi constructs are engineered to stably express the EGFP target gene using standard art known methods (Example 4). In addition the EGFP gene can be transiently transfected into GNAT-2 expressing and GNAT-2 non-expressing cell lines. Subsequently levels of EGFP expression in transfected cells is evaluated

using, for example, real-time RT PCR and fluorescent microscopy (Example 4). While albumin and GNAT-2 promoters are used a wide range of promoter sequences can be used, see for example, Figure 3. --

Please replace the heading for Example 5 with the following underlined heading:

-- Example 5: Transgenic ~~Annuals~~Animals --